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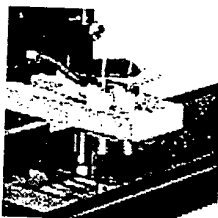
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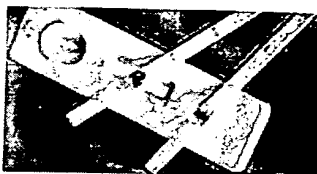
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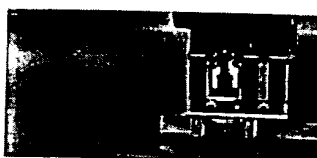
## Bio Dot Products

### Product's Market Segment

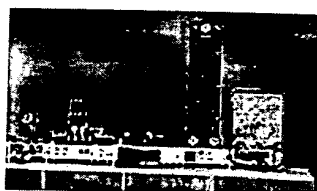
☐ Rapid biodiagnostic  
test Equipment



☐ Biosensor-Microfluidic  
Equipment



☐ Web Handling Equipment



☐  One Step One Solution  
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☐ Specifications Sheets  
*Technical Spec's - Printable*

Welcome to

**GeSiM** Gesellschaft für Silizium-Mikrosysteme mbH

GERMANY D-01454 Großberkmannsdorf

This page is optimized for 10:

Silicon / Glass Micromachining

Liquid Handling Systems

Flow-Trough-Systems

Nanoliter Dispensing Products

Microarrayer

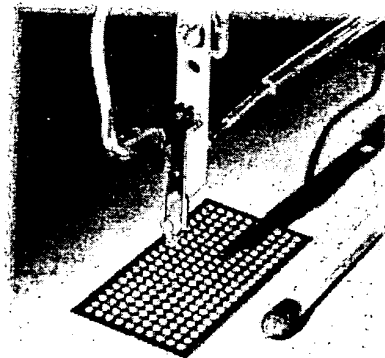
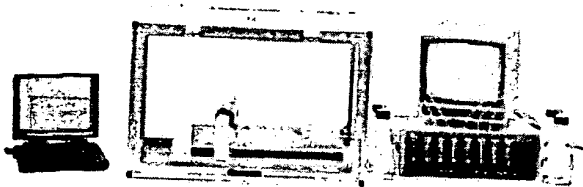
Flow Sensors

## *Liquidhandling in the Nanolitre-Range .....*

Nano-Plotter NP 1.2

Micro Dosage Products

Mi



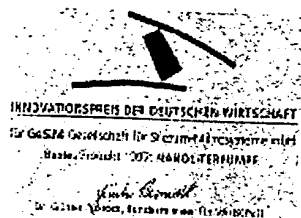
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Last Update: August 24, 2001

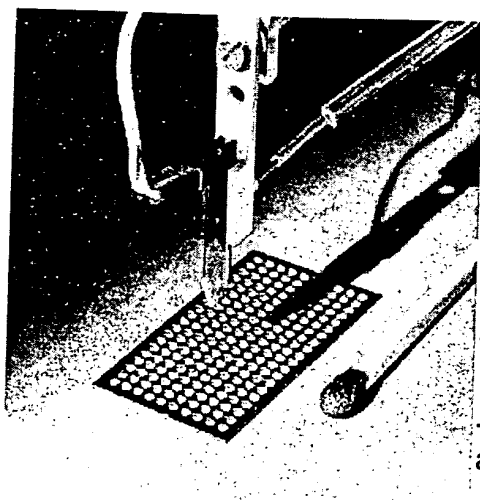
# GeSiM - Micro Pipettes / Applications

## Micro Pipettes

powered by piezoelectric actuators



*The piezoelectric micropipette was  
awarded by the  
German Government  
(Department of Economic Affairs) in 1997.*



- Delivery of drops as small as 0.03 nL
- Flow rates up to 600  $\mu\text{L}$  / min
- PC-control
- Compact design
- Resistant against many solvents and chemical substances

The GeSiM-micropipette SPIP (Standard Pipette) is a micromachined droplet dispenser with a unique design. The integrated piezodispenser is capable of generating droplets covering a volume range from 30 pL up to 2 nL per droplet (depending on the pipette type, sample properties and electrical parameters).

The device can be primed manually by pushing sample through a tubing connected to the inlet. After filling of the pumpchamber (0.8  $\mu\text{L}$ ) the pipette is ready for dispense. Automatic aspiration requires external support. A complete micro pipetting system equipped with a similar microdispenser is available. Please refer to the Nano-Plotter.

The piezoelectric pumps are suitable for precise delivery of fluids in the nanoliter range. By the drop on demand technique only the requested number of drops is delivered. The formation of a droplet can be repeated several thousand times per second to result in flow rates up to 600  $\mu\text{L}/\text{min}$ . A certain predefined number of drops may be pumped.

The deposition of drops is achieved without touching the target. They bridge a space of millimeter to centimeters through their kinetic energy. The compact design of the pump makes the integration at narrow sites and places with size restrictions possible.

Automatic operation (PC controlled) of the GeSiM micropipettes is achieved by the multi-dos unit.

## Fields of Application

The miniaturized dispensers can be used to fill smallest cavities, e.g. the wells of 1536 microtiter plates or even micromachined Nanotiterplates (see picture). There are several types of micropipettes available differing in dispense volume as well as in interconnecting parts. They can be integrated easily in standard laboratory environments.

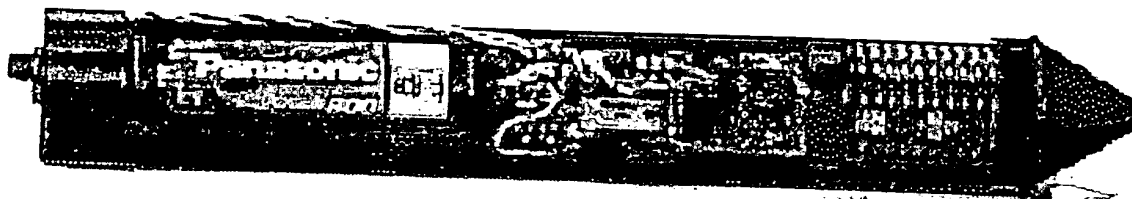
In most cases the GeSiM micropipettes are used in pharmaceutical drug research, genomics and biochemistry. A team of Harvard University has succeeded in building an inhouse microarrayer for DNA-chips using the SPIP from GeSiM.

Piezoelectric micro dispensers require certain ranges of viscosity and surface tension of the probes. Sample must not contain air bubbles. Also suspended matter which tends to clog might become a risk.

The following substances have been tested already:

- Acetic anhydride
- Acetone
- Acetonitrile
- Cyclohexanone
- Dextran suspensions
- Detergents (only at low concentration)
- Dichloromethane / trichloroacetic acid (98/2 %)
- N,N-Dimethylformamide (DMF)
- Dimethyl sulfoxide (DMSO)
- DNA (PCR, < 2 kb, < 3 µg/µl) in buffer
- DNA (plasmid, < 4 kb, < 1 µg/µl) in buffer
- Ethanol
- N- Fmoc-Ile 0,5 mmol in 2,5 ml DMF
- Glycerol (50 % in water)
- Isopropanol
- Iodine in tetrahydrofuran / pyridine / water (
- Methanol
- 1-Methyl-2-pyrrolidinone (NMP) 1-Meth
- Phosphoramidates in acetonitrile
- Silane, 2 - 3 % in propanol
- Tetrazole in acetonitrile
- Toluene

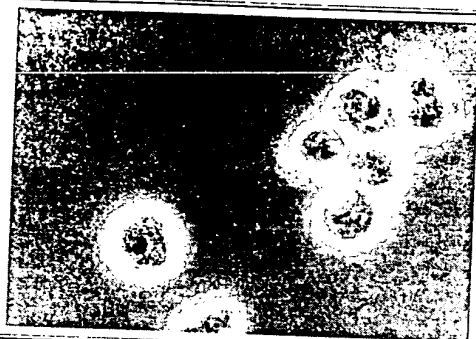
Ophthalmologic drugs often are applied to the conjunctiva by handpipettors. There are medical and economic disadvantages associated with this method. In most cases overdosing occurs as the minimum drug amount is limited to a couple of microliters. Only a few amount of the applied drug will take effect at the human eye.



*Courtesy  
of IMT  
Dresden*

A joint research project has led to a handheld device (battery powered) which is capable of submitting nanoliter amounts of the necessary drugs. A GeSiM micropipette connected to a drug reservoir is the core element of the system. The picture shows a preliminary version of the drug dispenser.

We deliver piezoelectric micropipettes to OEM users too. Please ask !



Cell research: Many types of biological cells can be treated with GeSiM micropipettes without significant damages.

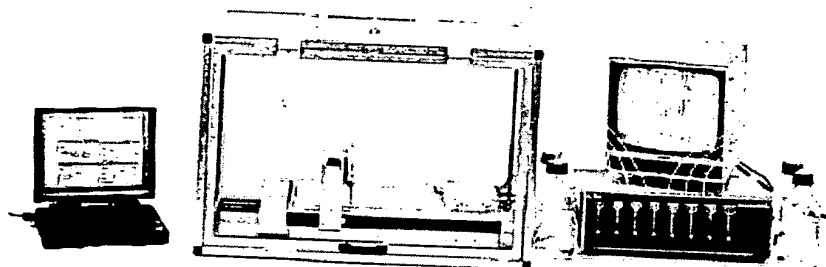
*(Coutesy of HKI Jena)*

Amazing opportunities for pharmaceutical research result from the combination of GeSiM micropipettes or micro pipetting systems with micromachined flow through systems. The micropipette can serve as an interface between substance libraries based on stocks of micro titer plates and application specific microfluidic flow through systems.

# GeSiM - The Nano-Plotter <sup>TM</sup> / Introduction

## Universal Micropipetting System with piezoelectric Tips

- Microarrays
- DNA-Diagnostics
- Biochip Preparation
- Biosensors
- Dilution Series



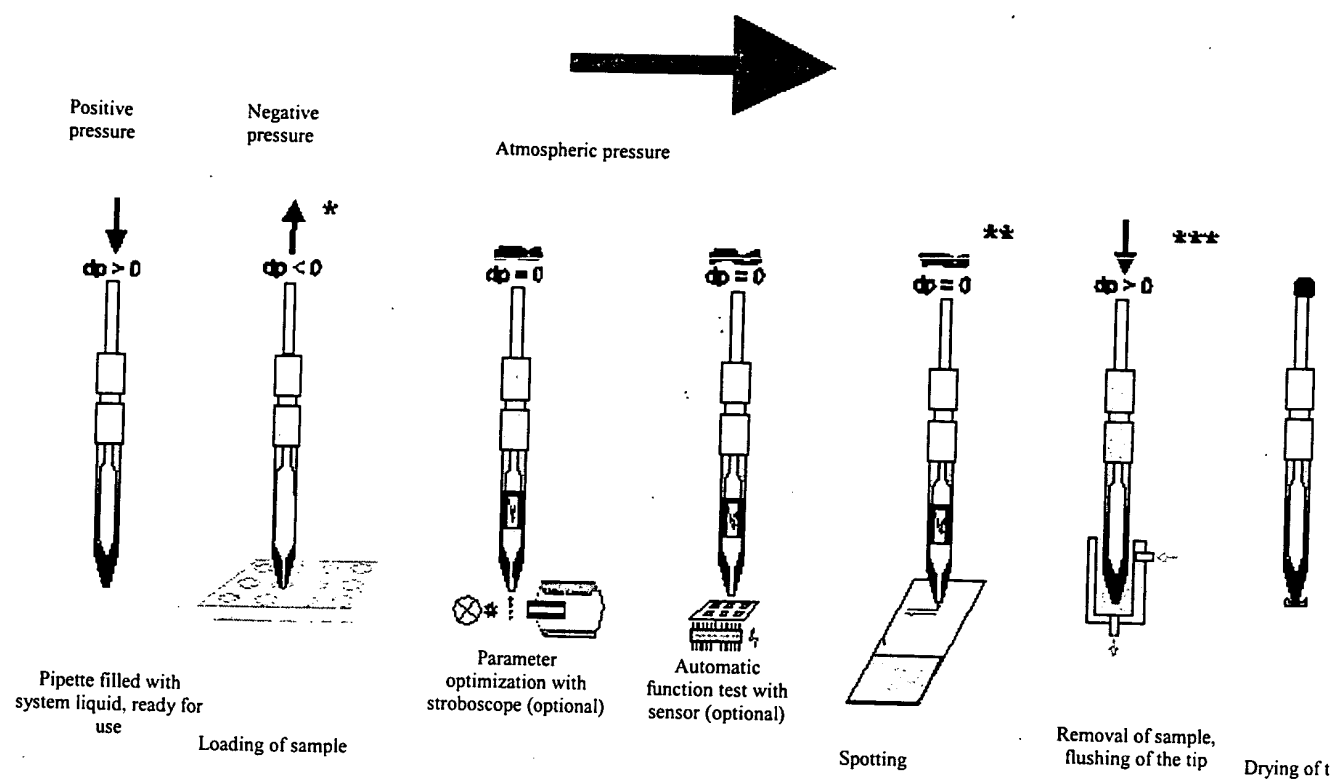
The Nano-Plotter <sup>TM</sup> (model 1.2) is suitable for pipetting tasks in the submicrolitre range (100 picolitres up to a few microlitres at each dosage position). The piezoelectric micropipettes dispense in accordance with the drop on demand principle and can be arranged at a pitch of 4.5 mm or 9 mm.

This versatile touchless dosage technology allows the immobilisation of extremely small spots on various solid surfaces as well as the addition of liquid samples to preloaded cavities.

### At a Glance

Handling of liquid sample from the picoliter up to the nanoliter range	Touchless, reproducible and drop by drop dosage of volumes from 0.1 nl up to several microliters
Completion of proven diluter technology with innovative piezoelectric micropipettes	Easy to use program generation supported by a graphical user interface
PC- controlled fast drives	Compact dimensions, Data transfer via RS232
Visual droplet control by stroboscope	After sales upgrades available
Microassays with the Nano-Tip	Microarrays with the Piko-Tip
Highest dispense yield 60 µl/s	Highest Array density 1.200/sqcm

Operating principle of the piezoelectric Nano-Plotter tips



\* Programmable Aspiration from 1  $\mu$ l stepwise (Step volume 0.1  $\mu$ l)

\*\* Dosage of a certain number of droplets of each tip, drop frequency up to 1000 Hz

\*\*\* The remaining sample can be removed at the waste position or can be put back to the related well of the microtiter plate



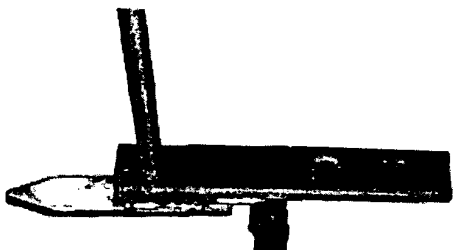
# GeSiM - Micro Pipettes / Pump Types and Technical Data

## Nanoliter Pumps

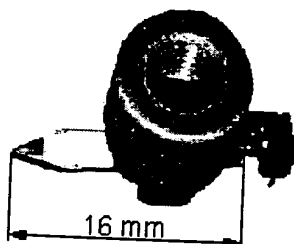
with piezoelectric actuators



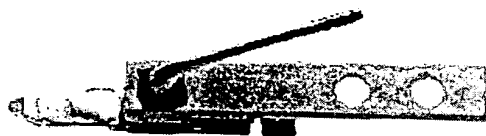
**Standard micro pipette SPIP with stainless steel inlet:**  
Outer diameter of connector 1.6 mm; ID 0,8 mm  
Suitable for connection to flexible tubing



**Standard pipette SPIP with PEEK-capillary:**  
15 cm length, OD 1/16", ID 0.25, 0.5 or 0.75 mm



**Standard pipette SPIP with 1/16" PEEK bushing:**  
Connection with 1/16" conventional HPLC -bushing



**Standard pipette SPIP with stainless steel capillary:**  
Inner diameter of tubes should be 0.6 mm or 0.7 mm



**High throughput pipette HDPIP:**  
Flow rates up to 600  $\mu$ l/min, connectors can be varied as in type SPIP

### Control parameter

Amplitude of voltage: 40 - 60 V

Impulse duration: 30 - 100  $\mu$ s

Frequency: up to 1000 Hz type SPIP, approx. 6000 Hz type HDPIP

### Pump delivery

Volume of single drops: 0.5 - 2 nl

Flow rate: up to 70  $\mu$ l/min type SPIP, up to 600  $\mu$ l/min type HDPIP

### Fluids to be pumped:

Water and aqueous solutions, organic solvents like ethanol, acetonitrile, DMSO, diluted acids, media with a high viscosity

may be pumped with a heated pump

### Precision of type SPIP:

100 drops (100 nl): CV < 2 %

### Size of pump

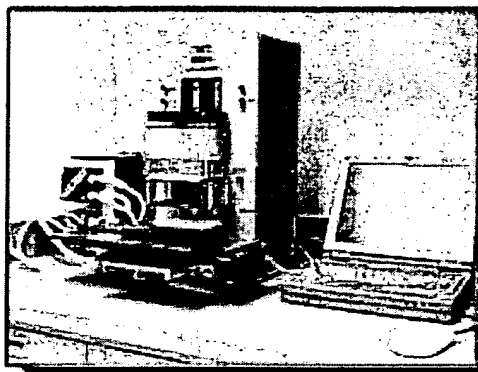
16 mm x 3 mm x 1,5 mm (L x W x H) bonded pump chip





**INNOVATIONS****LITERATURE REQUEST****TECHNICAL INFO****CONTACT ROBBINS****ENTER MAIL LIST****HOME****FEATURE ARTICLE****▲ New Ultra Hydra®-96 Dispenses to 10nl**

Jim Stanchfield, Ph.D.,  
Robbins Scientific, Sunnyvale CA



**Figure 1:** Hydra Microdispenser with Automated Plate Positioning System for dispensing into 96, 384 and 1536 plates.

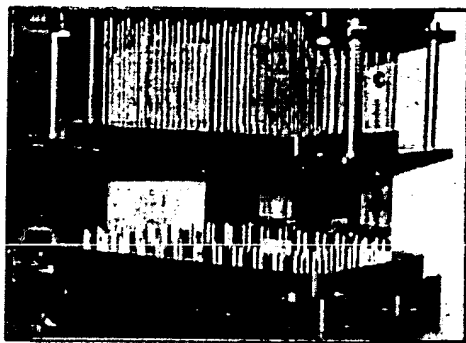
The march to ever smaller assay volumes and ever higher well density plates in High Throughput Screening (HTS) applications continues unabated. The reasons are simple.... squeezing more samples into a microplate reduces reagent consumption and labor. The end result is a drop in both per sample assay costs and processing time.

While some laboratories have successfully re-tooled for running assays in 384 well plates, the introduction of a 1536 well plate (Greiner, Frickenhausen, Germany and others) has made many screening groups re-assess their long term screening strategy.

Unfortunately, much of the equipment that works with 384 well plates (liquid handlers, plate readers etc.) is not capable of dealing with the demands of the new 1536 plates.

With a working volume of 5-10 $\mu$ l, a well opening of 1.70mm (Greiner), and center to center well spacing of 2.25mm, 1536 plates pose several significant challenges for use in HTS. First, assay conditions must be developed to generate a signal (typically fluorescence) that can be detected despite a nearly 30 fold reduction in assay volume from 96 well plates. Reading signals from the plate poses another set of challenges due to the number and density of the wells and the generally low signal generated. Despite these issues, new readers that reportedly can be used with 1536 plates are coming to market by LjL, (Sunnyvale, CA) and others. Lastly, automated liquid handling equipment must have the ability to dispense as little as 50nl of assay components into 96 or more wells at a time. The 50nl requirement is driven by the need to have a final concentration of DMSO (generally used as the medium for storing compounds) below 1%, assuming a working volume of 5 $\mu$ l per well in a 1536 well plate.

**Development of a Nanoliter 96 Channel Dispenser for use with 1536 Well Plates**

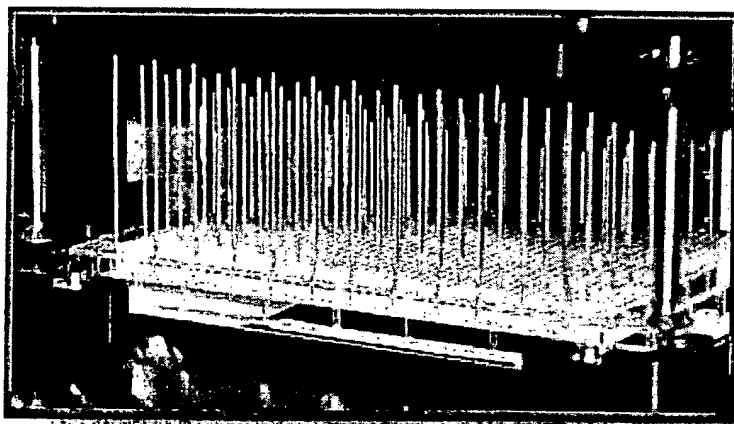


**Figure 2:** A metal plate with precision spaced pins is used to visually calibrate the plate positioning stage for dispensing into 1536 well plates.

Robbins has been working in close cooperation with emerging technology groups at several large pharmaceutical companies with the objective of perfecting the Hydra-96 microdispenser and its plate handling system for use with nanoliter dispensing into 1536 plate applications.

In early 1998, Robbins introduced an automated system for positioning source and target plates below the dispensing head of the Hydra (Click [here](#) for more information on the Automated Plate Positioning System).

The X-Y positioning of the stage can be adjusted in increments of 5 microns, which is more than sufficient for correct positioning of 1536 well plates. A method for calibrating and testing the system for use with 1536 well plates was developed using a precision machined "pin target" that emulates the position of the wells in a 1536 plate. This target is used for fine adjustment of the stage position relative to the needle array (Figure 2). Wizard based software controls the movement of the stage and can be used with the pin target to simplify the calibration routine. All Hydras equipped with 100 $\mu$ l syringes and the Automated Plate Positioning System are certified and tested at the factory for dispensing into 1536 well plates.



**Figure 3:** Hydra-96 and -384 Microdispensers are routinely used for dispensing reagents into 1536 well plates.

## New 10 $\mu$ l Syringe For Nanoliter Dispensing

After solving the mechanical requirements of positioning and dispensing into 1536 well plates, we turned our attention to designing a new syringe for the Hydra that would extend the dispensing capability of the instrument below the 100nl limit of the 100 $\mu$ l syringes.

Knowing the minimum plunger travel distance achieved on the Hydra, we calculated that a minimum dispense volume of 10nl should be obtainable using a 10 $\mu$ l syringe without changes to the syringe drive system. The design of the new 10 $\mu$ l syringe for the Hydra is shown in Figure 4. It has the same outside dimensions as the 100 $\mu$ l syringe. One concern we had in designing the new syringe was that the wire-like plunger used with the syringe would bend.

However, with routine usage in our laboratory, we have not had a single occurrence of the plungers bending or failing.

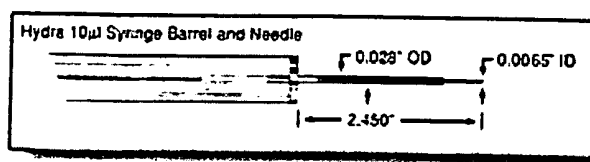


Figure 4: The new 10µl syringe developed by Robbins has a special "stepped" narrow diameter needle tip for improved nanoliter dispensing performance.

Another challenge when developing the new syringe was to design a needle that would yield very fine droplets yet be robust enough to withstand routine usage. Starting with a needle that has large outside diameter and a small inner diameter, we applied a special machining process to reduce the diameter of the end of the needle tip to form a fine, thin section long enough to reach the bottom of a 1536 well plate. After polishing, the needles are coated with Teflon to ensure even drop formation at the ends.

### Benchmarking the Minimum Dispense Volume of the Hydra-96 Microdispenser

The first tests performed on a Hydra equipped with the new 10µl syringes were designed to determine the minimum volume of aqueous or DMSO solutions that can be reliably dispensed into a plate containing buffer. Using concentrated fluorescein as a test solution, plates were generated (after priming) with programmed dispense volumes ranging from 10nl to 100nl and the coefficient of variation (C.V.) across each plate determined for each dispense volume. These data are shown in Tables 1 and 2. Using an aqueous test solution and plates containing buffer, the Ultra Hydra-96 showed a plate C.V. of under 10% at 10nl and a C.V. below 5% at volumes of 30nl and above. The C.V.'s generated when dispensing DMSO into plates containing buffer plates were nearly identical.

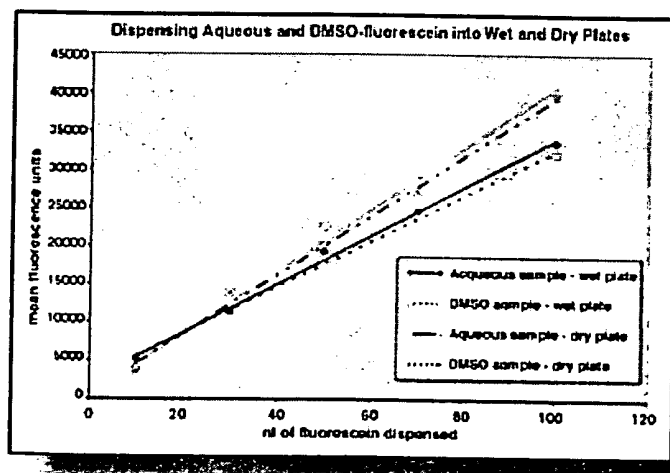


Table 1: Linearity of dispense of the Ultra Hydra-96 using wet and dry plates.

Dispensing onto dry plates is frequently required in HTS when adding test compounds or unstable reagents into the plate prior to the addition of buffer or other assay components. Using the same conditions described previously, test

volumes were deposited onto the bottom of the plates and buffer added. The test results shown in Table 2 clearly show that the Ultra Hydra-96 can deliver 100% DMSO solutions onto the bottom of a dry plate at volumes of 50nl and above with a C.V. below 10%.

	Volume Dispensed(nl)	Wet Plate MRF	%C.V.	Dry Plat MRF	%C.V.
Aqueous	10	5279	8.59	3839	46.27
	30	11347	4.40	11657	27.75
	50	19093	2.94	22509	16.19
	70	24567	2.55	29535	6.39
	100	33586	2.98	39558	7.24
DMSO	10	5239	11.11	3635	51.67
	30	11382	4.28	13804	3.57
	50	18332	2.48	19742	4.70
	70	23727	2.10	27206	8.09
	100	32082	1.90	39577	5.37

Table 2: Dispensing Precision of the Ultra Hydra-96 using Wet and Dry Plates.

## Conclusion

Test results from a Hydra-96 equipped with 10µl syringes show the instrument can dispense to 10nl when using a wet plate and to 50nl using a dry plate. These findings are significant not only for existing HTS groups using standard 96 or 384 well microplates but are even more important for those looking for a liquid handling system for dispensing into 1536 well plates. The Ultra Hydra-96 Microdispenser will be available for delivery in early 1999.

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